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(54) Title: METABOLIC KINASE MODULATORS AND METHODS OF USE AS PESTICIDES

(57) Abstract: This invention relates to compounds that can be used as pesticides, in particular their use as agents in the control of pests for crop protection, human and animal health, and home and garden applications. More specifically, this invention relates to the use of compounds that modulate metabolic kinase pathways of pests, in particular that inhibit the ethanolamine kinase pathways of pests, the disruption of which proves lethal.

Metabolic Kinase Modulators and Methods of Use as Pesticides

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional patent application 60/551,428 filed on March 8, 2004, entitled "Metabolic Kinase Modulators and Methods of Use," naming McMillan, Kirk as the inventor; which is hereby incorporated by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention relates to compounds that can be used as pesticides, in particular their use as agents in the control of pests for crop protection, human and animal health, and home and garden applications. More specifically, this invention relates to the use of compounds that modulate metabolic kinase pathways of pests, in particular that inhibit the ethanolamine kinase pathways of pests, the disruption of which proves lethal.

Summary of Related Art

[0003] The phospholipids phosphatidylethanolamine and phosphatidylcholine are the primary phospholipids comprising cellular membranes. Phosphatidylethanolamine (PE) is the predominant lipid in *Drosophila*. Lipid composition and its regulation can affect many cellular processes including lipid-derived second messenger systems, function of membrane proteins such as ion channels, and membrane fusion and trafficking. The mechanism of these effects remains unknown. Ethanolamine kinase (EK) catalyzes the initial step in the CDP-ethanolamine pathway for phosphatidylethanolamine synthesis.

[0004] Disruption of *Drosophila melanogaster* ethanolamine kinase, also known as *easily shocked* (*eas*), results in flies which are paralyzed following a mechanical shock. Paralysis is due to a neuronal excitability defect believed to be the result of reduced PE & altered membrane phospholipid composition. (Pavlidis et al. 1994) Inhibition of EK in the insect is hypothesized to alter the phospholipid membrane composition of the insects resulting in locomotor defects and possibly paralysis.

[0005] Pesticide development has traditionally focused on the altering the chemical and physical properties of the pesticide itself, a relatively time-consuming and expensive process. As a consequence, efforts have been concentrated on the modification of pre-existing, well-validated compounds, rather than on the development of new pesticides. The resulting pesticide market and more specifically the insecticide market is comprised of compounds that act on pests through a limited number of mechanisms. With limited mechanisms in which to control pests, resistant populations quickly develop for which there are no means of control. Therefore, the need exists in the art for new pesticidal compounds that act through new mechanisms, are safer, more selective, and more efficient than currently available pesticides. The present invention addresses this need by providing novel pesticide compounds for pests, such as insects (including dipteran, homopteran and lepidopteron species), by providing methods of identifying compounds that bind to and modulate the activity of such targets.

[0006] The development of EK inhibitors as a pesticide targets is supported by the genetic and biochemical evaluation of the *Drosophila melanogaster* mutants of the *easily shocked* (*eas*) locus. The disrupted gene product of the *eas* locus was cloned and found to encode for ethanolamine kinase. There are five mutants of the *eas* locus in *Drosophila*, which have been phenotypically characterized. eas^{1}, eas^{2} and eas^{P372} are all behavioral recessive null alleles. eas^{PL48} and eas^{PL103} are loss of function recessive lethal alleles.

[0007] eas^{1} and eas^{2} contain a 2 bp deletion at nucleotide 1004-1005 of the EK cDNA causing a frameshift mutation, which introduces a stop codon at nucleotide position 1078. The resulting predicted protein would contain the first 260 amino acids of the *eas* product and lack the conserved kinase domain. eas^{P372} has a P-element insertion in the 5' non-coding region of the gene at nucleotide 27. (Pavlidis et al 1994) In addition to being a behavioral mutant, the chromosome is also recessive lethal, but it is unknown if the lethality maps to the *eas* mutation. A heat-shock rescue construct ($eas^{hs.PP}$) rescues eas^{2} but not the lethality of eas^{P372} (Pavlidis et al 1994) suggesting the lethality is unlinked.

[0008] The behavioral phenotype of these alleles is as follows: Flies become paralyzed when exposed to 10 seconds of vortexing. A brief bang causes a period of hyperactivity lasting 1-2 seconds, during which flies fall over and vigorously flap their wings, shake and bend their legs, and flex their abdomens. The activity rapidly gives way to paralysis. Paralysis is characterized by a relaxed posture of the wings, legs, body and proboscis. After 20-30s, post-paralysis hyperactivity begins, characterized by massive uncoordinated

motor activity similar to that before the paralysis phase. The paralysis was phenocopied with electrophysiological experiments in which seizure like activity was observed in dorsal longitudinal muscles following a brief electrical stimulus. In addition, *Drosophila eas* mutants show a loss of ethanolamine kinase activity and in whole animal assays an altered PE/PC ratio 2.31 compared to 2.80 for wild type. (Pavlidis et al 1994) These results indicate that these mutants have hyper-excitable neuronal properties and suggest that this is due to altered membrane lipid composition. Therefore, inhibitors of EK could lead to similar hyper-excitable neurons that may result in loco-motor defects or paralysis. Any loss of loco-motor control in a field setting will result in an increase in mortality, as the animals are unable to escape the heat of the day and gain access to proper nutrients and water.

[0009] While the behavioral mutants are viable two additional alleles eas^{PL48}, and eas^{PL103} have been characterized as loss of function recessive lethal alleles. These alleles were identified in a p-element insertional mutagenesis screen of the X-chromosome (Bourbon et al. 2002). Linkage of the lethality to the insertion has not been confirmed. However, 82% of the lines tested for linkage were confirmed (91/111), supporting that the lethality of 1 or both of these lines maybe linked to the p-element insertion. The lethality of these alleles supports that loss of EK activity will result in non-viable animals.

[0010] In addition the p-element used to generate eas^{PL48} contains a lacZ enhancer trap allowing for observation of expression of disrupted genes. Expression was observed in third instar larvae in the brain, salivary gland, midgut and imaginal discs. The larval brain expression is consistent with the observed behavioral phenotype.

[0011] Unlike many mammalian EKs, which show substrate promiscuity for choline, non-mammalian EKs, such as the *Drosophila* EK, is specific for ethanolamine. This substrate specificity may indicate a structural difference between the mammalian and non-mammalian forms, such as insect forms, allowing for the development of non-mammalian specific inhibitors.

[0012] Accordingly, the identification of small-molecule compounds that modulate, and more specifically inhibit, the activity of metabolic kinases, particularly EK, is desirable as a means to protect crops, animals and humans, and home and garden materials from pests and is an object of this invention.

[0013] References: Pavlidis et al. (1994) *Cell* 79 :23-33 ; Pavlidis et al. (1995) *J. Neurosci.* 15 :5810-5819; Porter et al. (1990) *J.Biol. Chem.* 265:414-422; Kim et al. (1999) *J. Biol. Chem.* 274:14857-14866; Draus et al. (1990) *Biochim. Biophys. Acta* 1045:195-205; Ishidate (1997) *Biochim. Biophys. Acta* 1348:70-78. Ganetzky and Wu (1982) *Genetics* 100(4):597-614. Bourbon et al. (2002) *Mech. of Dev.* 110:71-83.

SUMMARY OF THE INVENTION

[0014] In one aspect, the present invention provides compounds and compositions for modulating the activity of metabolic kinases present in pests, particularly EK. In particular, the present invention provides for compounds and compositions for inhibiting the activity of metabolic kinases present in pests, particularly EK.

[0015] In another aspect, the invention provides for methods of controlling pests utilizing the compounds and pharmaceutical compositions thereof.

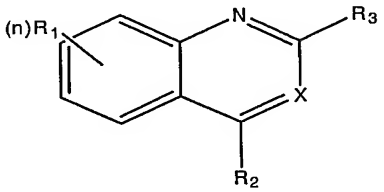
[0016] In yet another aspect, the invention also provides kits comprising one or more containers filled with one or more of the ingredients of the compounds and/or compositions of the present invention. Such kits can also include, for example, other compounds and/or compositions (e.g., insecticides, attractants, sterilizing agents, acaricides, nematicides, fungicides, growth-regulating substances or herbicides), a device(s) for administering the compounds and/or compositions, and written instructions for use of the kit to control pests.

[0017] These and other features and advantages of the present invention will be described in more detail below with reference to the associated drawings.

DETAILED DESCRIPTION OF THE INVENTION

[0018] The compounds and compositions of the present invention are used to control pests for crop protection, human and animal health and protection of home and garden materials.

[0019] The present invention comprises a composition, which comprises a carrier and an effective amount of at least one compound according to Formula **I**,



I

or an acceptable salt or hydrate thereof, wherein,

each of R^1 , R^2, R^3 are independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-NR^5R^5$, $-S(O)_{0-2}R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-N(R^5)SO_2R^5$, $-N(R^5)C(O)R^5$, $-N(R^5)CO_2R^5$, $-C(O)R^5$, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, and optionally substituted arylalkyl;

X is CR^4 or N;

each of R^4 and R^5 are independently selected from H, optionally substituted C_{1-10}alkyl, optionally substituted C_{1-10}alkoxy, optionally substituted aryl, optionally substituted aryl-C_{1-10}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl-C_{1-10}alkyl; and

n is an integer from 0-4.

[0020] In one example, the composition is according to paragraph [0019], wherein X is CR^4.

[0021] In one example, the composition is according to paragraph [0020], wherein X is CH.

[0022] In another example, the composition is according to paragraph [0021], wherein n is 1.

[0023] In another example, the composition is according to paragraph [0021], wherein n is 2.

[0024] In another example, the composition is according to paragraph [0022], wherein R^1 is halogen.

[0025] In another example, the composition is according to paragraph [0024], wherein R^1 is chlorine.

[0026] In another example, the composition is according to paragraph [0022], wherein R^1 is alkoxy.

[0027] In another example, the composition is according to paragraph [0022], wherein R^1 is methyl sulfate.

[0028] In another example, the composition is according to paragraph [0021], wherein R^2 is lower alkyl.

[0029] In another example, the composition is according to paragraph [0028], wherein R^2 is methyl.

[0030] In another example, the composition is according to paragraph [0021], wherein R^3 is optionally substituted heterocyclyl.

[0031] In another example, the composition is according to paragraph [0030], wherein R^3 is 1-methyl-[1, 4]diazepane.

[0032] In another example, the composition is according to paragraph [0019], wherein the compound is selected from Table 1. The compounds in Table 1 are commercially available. Compound of entry No. 3 has CAS Registration No. 418790-20-2 and the remaining entries are available from ChemBridge Research Laboratories 16981 Via Tazon, Suite K and ChemDiv, Inc. 11558 Sorrento Valley Road, Suite 5 San Diego, CA 92121 USA. Other compounds of Formula I would be known to those skilled in the chemical arts.

Table 1

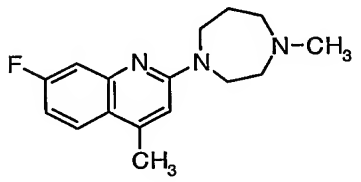
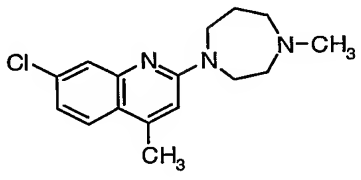
Entry	Name	Structure
1	7-fluoro-4-methyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	
2	7-chloro-4-methyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	

Table 1

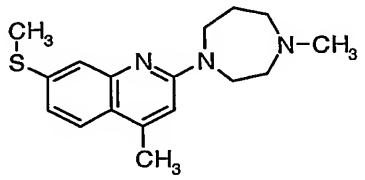
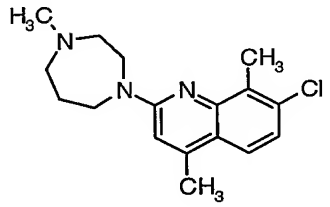
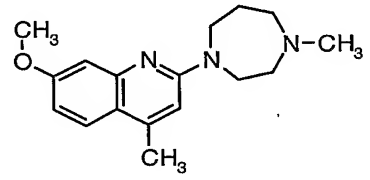
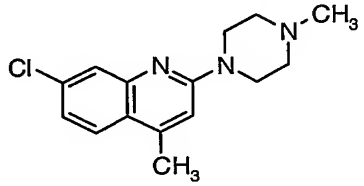
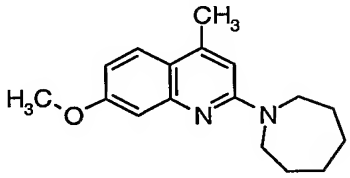
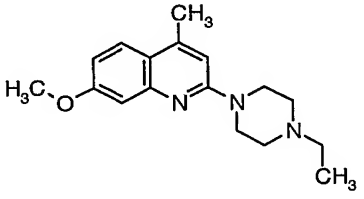
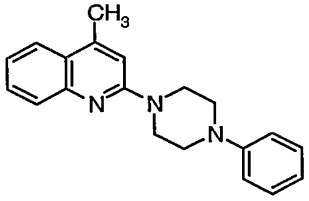
Entry	Name	Structure
3	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-7-(methylthio)quinoline	
4	7-chloro-4,8-dimethyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	
5	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-7-(methyloxy)quinoline	
6	7-chloro-4-methyl-2-(4-methylpiperazin-1-yl)quinoline	
7	2-azepan-1-yl-4-methyl-7-(methyloxy)quinoline	
8	2-(4-ethylpiperazin-1-yl)-4-methyl-7-(methyloxy)quinoline	
9	4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	

Table 1

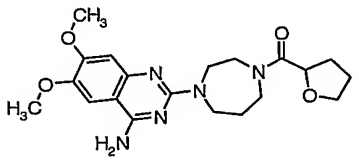
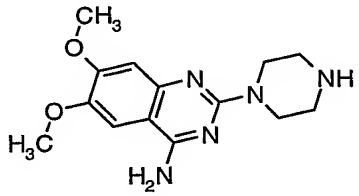
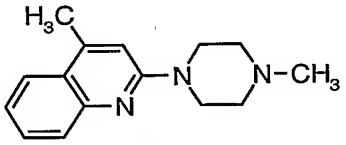
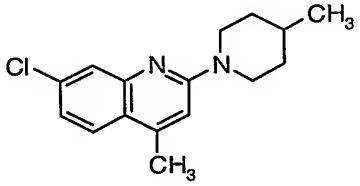
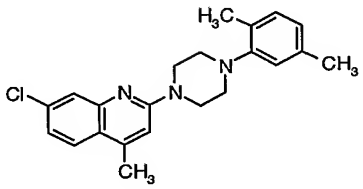
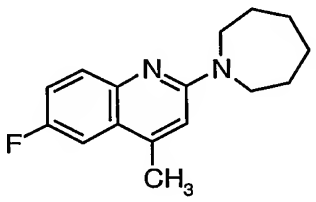
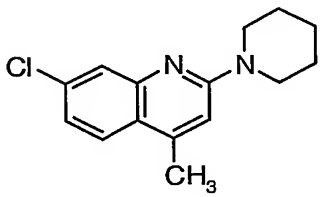
Entry	Name	Structure
10	6,7-bis(methyloxy)-2-[4-(tetrahydrofuran-2-ylcarbonyl)-1,4-diazepan-1-yl]quinazolin-4-amine	
11	6,7-bis(methyloxy)-2-piperazin-1-ylquinazolin-4-amine	
12	4-methyl-2-(4-methylpiperazin-1-yl)quinoline	
13	7-chloro-4-methyl-2-(4-methylpiperidin-1-yl)quinoline	
14	7-chloro-2-[4-(2,5-dimethylphenyl)piperazin-1-yl]-4-methylquinoline	
15	2-azepan-1-yl-6-fluoro-4-methylquinoline	
16	7-chloro-4-methyl-2-piperidin-1-ylquinoline	

Table 1

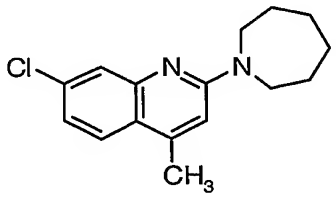
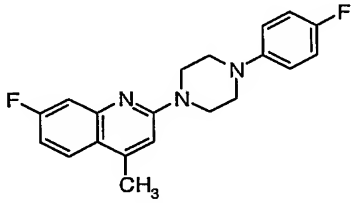
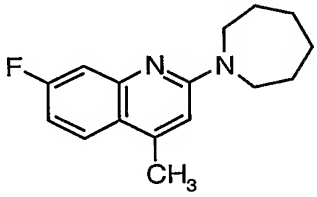
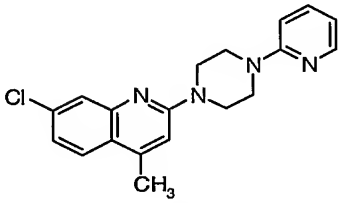
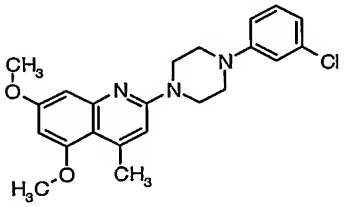
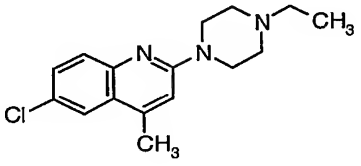
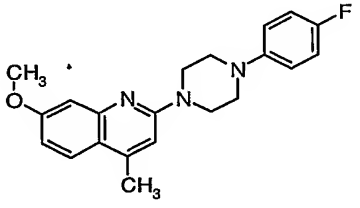
Entry	Name	Structure
17	2-azepan-1-yl-7-chloro-4-methylquinoline	
18	7-fluoro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	
19	2-azepan-1-yl-4-methyl-8-(methyloxy)quinoline	
20	7-chloro-4-methyl-2-(4-pyridin-2-ylpiperazin-1-yl)quinoline	
21	2-[4-(3-chlorophenyl)piperazin-1-yl]-4-methyl-5,7-bis(methyloxy)quinoline	
22	6-chloro-2-(4-ethylpiperazin-1-yl)-4-methylquinoline	
23	2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methyl-7-(methyloxy)quinoline	

Table 1

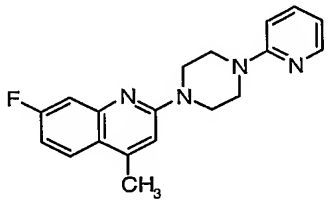
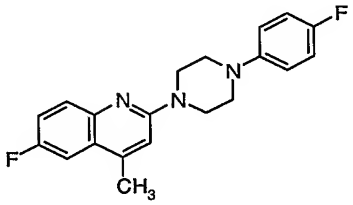
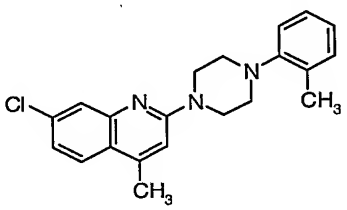
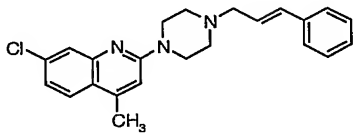
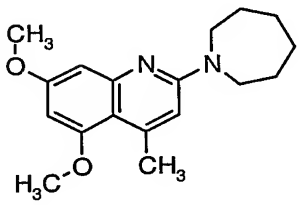
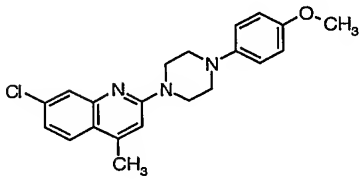
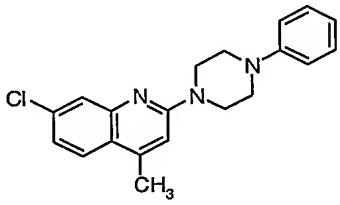
Entry	Name	Structure
24	7-fluoro-4-methyl-2-(4-pyridin-2-ylpiperazin-1-yl)quinoline	
25	6-fluoro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	
26	7-chloro-4-methyl-2-[4-(2-methylphenyl)piperazin-1-yl]quinoline	
27	7-chloro-4-methyl-2-{4-[(2E)-3-phenylprop-2-en-1-yl]piperazin-1-yl}quinoline	
28	2-azepan-1-yl-4-methyl-5,7-bis(methyloxy)quinoline	
29	7-chloro-4-methyl-2-{4-[4-(methyloxy)phenyl]piperazin-1-yl}quinoline	
30	7-chloro-4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	

Table 1

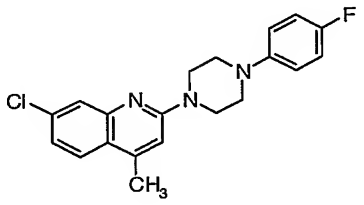
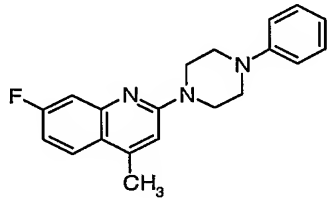
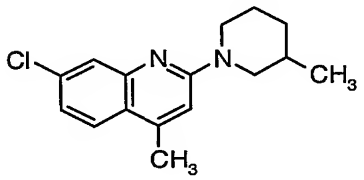
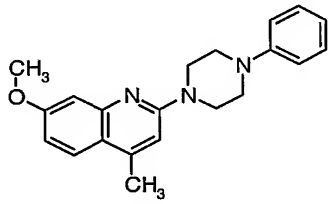
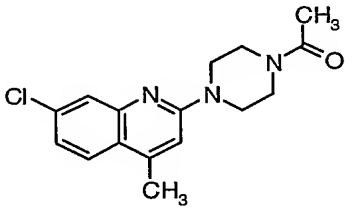
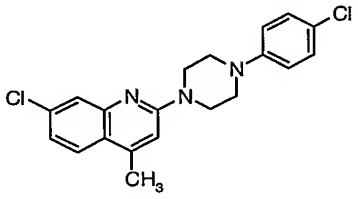
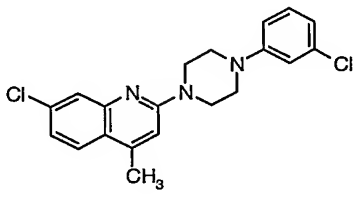
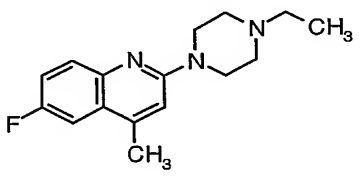
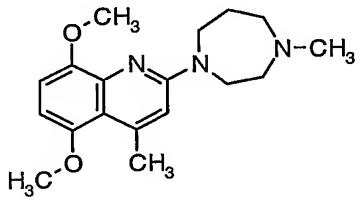
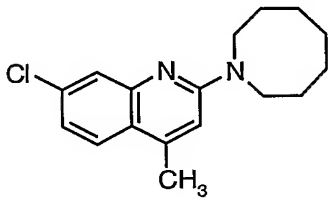
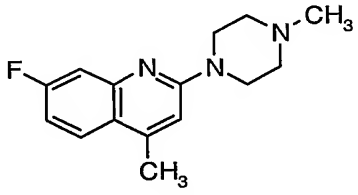
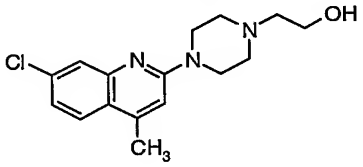
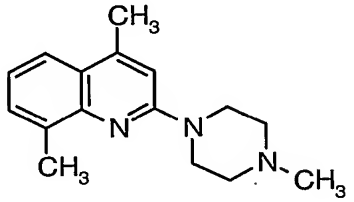
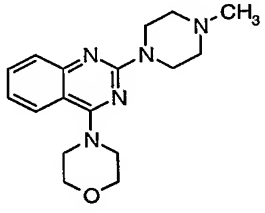
Entry	Name	Structure
31	7-chloro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	
32	7-fluoro-4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	
33	7-chloro-4-methyl-2-(3-methylpiperidin-1-yl)quinoline	
34	4-methyl-7-(methyloxy)-2-(4-phenylpiperazin-1-yl)quinoline	
35	2-(4-acetylpiperazin-1-yl)-7-chloro-4-methylquinoline	
36	7-chloro-2-[4-(4-chlorophenyl)piperazin-1-yl]-4-methylquinoline	
37	7-chloro-2-[4-(3-chlorophenyl)piperazin-1-yl]-4-methylquinoline	

Table 1

Entry	Name	Structure
38	2-(4-ethylpiperazin-1-yl)-6-fluoro-4-methylquinoline	
39	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-5,8-bis(methyloxy)quinoline	
40	2-azocan-1-yl-7-chloro-4-methylquinoline	
41	7-fluoro-4-methyl-2-(4-methylpiperazin-1-yl)quinoline	
42	2-[4-(7-chloro-4-methylquinolin-2-yl)piperazin-1-yl]ethanol	
43	4,8-dimethyl-2-(4-methylpiperazin-1-yl)quinoline	
44	2-(4-methylpiperazin-1-yl)-4-morpholin-4-ylquinazoline	

[0033] Another aspect of the invention is a method of modulating the activity of metabolic kinases in pests, the method comprising administering to a pest an effective amount of a formulation comprising at least one example of the composition according to any of paragraphs [0019]-[0032].

[0034] Another aspect of the invention is the method according to paragraph [0033], wherein the kinase is EK.

[0035] Another aspect of the invention is the method according to paragraph [0034], wherein modulating the activity of the kinase comprises inhibition of the kinase.

[0036] Another aspect of the invention is a method of controlling pests, the method comprising administering to a pest an effective amount of the composition according to any of paragraphs [0019]-[0032] or the formulation according to paragraph [0033].

[0037] Another aspect of the invention is a kit comprising one or more containers filled with one or more of the compounds and/or compositions of according to any of paragraphs [0019]-[0032] or the formulation according to paragraph [0033].

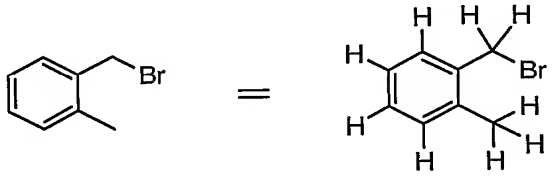
Definitions

[0038] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise or they are expressly defined to mean something different.

[0039] The symbol "-" means a single bond, "=" means a double bond, "≡" means a triple bond. The symbol "  " refers to a group on a double-bond as occupying either position on the terminus of a double bond to which the symbol is attached; that is, the geometry, *E*- or *Z*-, of the double bond is ambiguous. When a group is depicted removed from its parent formula, the "  " symbol will be used at the end of the bond which was theoretically cleaved in order to separate the group from its parent structural formula.

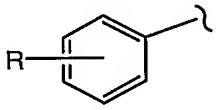
[0040] When chemical structures are depicted or described, unless explicitly stated otherwise, all carbons are assumed to have hydrogen substitution to conform to a valence of four. For example, in the structure on the left-hand side of the schematic below there are nine hydrogens implied. The nine hydrogens are depicted in the right-hand structure.

Sometimes a particular atom in a structure is described in textual formula as having a hydrogen or hydrogens as substitution (expressly defined hydrogen), for example, $-CH_2CH_2-$. It is understood by one of ordinary skill in the art that the aforementioned descriptive techniques are common in the chemical arts to provide brevity and simplicity to description of otherwise complex structures.



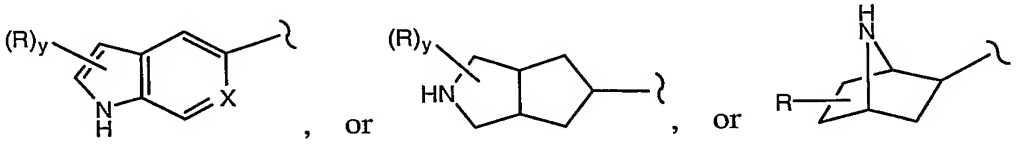
[0041] In this application, some ring structures are depicted generically and will be described textually. For example, in the schematic below, if in the structure on the left, ring A is used to describe a "spirocyclyl," then if ring A is cyclopropyl, there are at most four hydrogens on ring A (when "R" can also be -H). In another example, as depicted on the right side of the schematic below, if ring B is used to describe a "phenylene" then there can be at most four hydrogens on ring B (assuming depicted cleaved bonds are not C-H bonds).

[0042] If a group "R" is depicted as "floating" on a ring system, as for example in the formula:



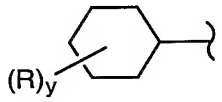
then, unless otherwise defined, a substituent "R" may reside on any atom of the ring system, assuming replacement of a depicted, implied, or expressly defined hydrogen from one of the ring atoms, so long as a stable structure is formed.

[0043] If a group "R" is depicted as floating on a fused ring system, as for example in the formulae:

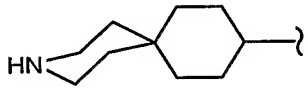


then, unless otherwise defined, a substituent "R" may reside on any atom of the fused ring system, assuming replacement of a depicted hydrogen (for example the -NH- in the formula above), implied hydrogen (for example as in the formula above, where the hydrogens are not shown but understood to be present), or expressly defined hydrogen (for example where in the formula above, "X" equals =CH-) from one of the ring atoms, so long as a stable structure is formed. In the example depicted, the "R" group may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula depicted above, when y is 2 for example, then the two "R's" may reside on any two atoms of the ring system, again assuming each replaces a depicted, implied, or expressly defined hydrogen on the ring.

[0044] When a group "R" is depicted as existing on a ring system containing saturated carbons, as for example in the formula:



where, in this example, "y" can be more than one, assuming each replaces a currently depicted, implied, or expressly defined hydrogen on the ring; then, unless otherwise defined, where the resulting structure is stable, two "R's" may reside on the same carbon. A simple example is when R is a methyl group; there can exist a geminal dimethyl on a carbon of the depicted ring (an "annular" carbon). In another example, two R's on the same carbon, including that carbon, may form a ring, thus creating a spirocyclic ring (a "spirocyclyl" group) structure with the depicted ring as for example in the formula:



[0045] "Alkyl" is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof, inclusively. For example, "C_8 alkyl" may refer to an *n*-octyl, *iso*-octyl, cyclohexylethyl, and the like. Lower alkyl refers to alkyl groups of from one to six carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *s*-butyl, *t*-butyl, isobutyl, pentyl, hexyl and the like. Higher alkyl refers to alkyl groups containing more that eight carbon atoms. Exemplary alkyl groups are those of C_{20} or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from three to thirteen carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl, adamantyl and the like. In this application, alkyl

refers to alkanyl, alkenyl, and alkynyl residues (and combinations thereof); it is intended to include cyclohexylmethyl, vinyl, allyl, isoprenyl, and the like. Thus, when an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of *carbons* are intended to be encompassed; thus, for example, either "butyl" or "C_4alkyl" is meant to include *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, isobutenyl and but-2-yne radicals; and for example, "propyl" or "C_3alkyl" each include *n*-propyl, propenyl, and isopropyl. Otherwise, if alkenyl and/or alkynyl descriptors *are used* in a particular definition of a group, for example "C_4alkyl" along "C_4alkenyl," then C_4alkenyl geometric isomers are not meant to be included in "C_4alkyl," but other 4-carbon isomers are, for example C_4alkynyl. For example, a more general description, intending to encompass the invention as a whole may describe a particular group as "C_{1-8}alkyl" while a preferred species may describe the same group as including, "C_{1-8}alkyl," "C_{1-6}alkenyl" and "C_{1-5}alkynyl."

[0046] "Alkylene" refers to straight or branched chain divalent radical consisting solely of carbon and hydrogen atoms, containing no unsaturation and having from one to ten carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene and the like. Alkylene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, fully saturated. Examples of alkylene include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), dimethylpropylene ($-CH_2C(CH_3)_2CH_2-$), and cyclohexylpropylene ($-CH_2CH_2CH(C_6H_{13})$).

[0047] "Alkylidene" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms, having from two to ten carbon atoms, for example, ethylidene, propylidene, *n*-butylidene, and the like. Alkylidene is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, double bond unsaturation. The unsaturation present includes at least one double bond.

[0048] "Alkylidyne" refers to a straight or branched chain unsaturated divalent radical consisting solely of carbon and hydrogen atoms having from two to ten carbon atoms, for example, propylid-2-ynyl, *n*-butylid-1-ynyl, and the like. Alkylidyne is a subset of alkyl, referring to the same residues as alkyl, but having two points of attachment and, specifically, triple bond unsaturation. The unsaturation present includes at least one triple bond.

[0049] Any of the above radicals, "alkylene," "alkylidene" and "alkylidyne," when optionally substituted, may contain alkyl substitution which itself contains unsaturation. For example, 2-(2-phenylethynyl-but-3-enyl)-naphthalene (IUPAC name) contains an *n*-butylid-3-ynyl radical with a vinyl substituent at the 2-position of said radical.

[0050] "Alkoxy" or "alkoxyl" refers to the group -O-alkyl, for example including from one to eight carbon atoms of a straight, branched, cyclic configuration, unsaturated chains, and combinations thereof attached to the parent structure through an oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to six carbons.

[0051] "Substituted alkoxy" refers to the group -O-(substituted alkyl), the substitution on the alkyl group generally containing more than only carbon (as defined by alkoxy). One exemplary substituted alkoxy group is "polyalkoxy" or -O-optionally substituted alkylene-optionally substituted alkoxy, and includes groups such as $-OCH_2CH_2OCH_3$, and glycol ethers such as polyethyleneglycol and $-O(CH_2CH_2O)_xCH_3$, where x is an integer of between about two and about twenty, in another example, between about two and about ten, and in a further example between about two and about five. Another exemplary substituted alkoxy group is hydroxyalkoxy or $-OCH_2(CH_2)_yOH$, where y is for example an integer of between about one and about ten, in another example y is an integer of between about one and about four.

[0052] "Acyl" refers to groups of from one to ten carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, *t*-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to six carbons.

[0053] "α-Amino Acids" refer to naturally occurring and commercially available amino acids and optical isomers thereof. Typical natural and commercially available α-amino acids are glycine, alanine, serine, homoserine, threonine, valine, norvaline, leucine, isoleucine, norleucine, aspartic acid, glutamic acid, lysine, omithine, histidine, arginine, cysteine, homocysteine, methionine, phenylalanine, homophenylalanine, phenylglycine, ortho-tyrosine, meta-tyrosine, para-tyrosine, tryptophan, glutamine, asparagine, proline and hydroxyproline. A "side chain of an α-amino acid" refers to the radical found on the

α-carbon of an α-amino acid as defined above, for example, hydrogen (for glycine), methyl (for alanine), benzyl (for phenylalanine), and the like.

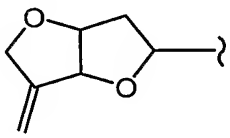
[0054] "Amino" refers to the group $-NH_2$. "Substituted amino," refers to the group -N(H)R or –N(R)R where each R is independently selected from the group: optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted heterocyclyl, acyl, carboxy, alkoxycarbonyl, sulfanyl, sulfinyl and sulfonyl, for example, diethylamino, methylsulfonylamino, and furanyl-oxy-sulfonamino.

[0055] "Aryl" refers to aromatic six- to fourteen-membered carbocyclic ring, for example, benzene, naphthalene, indane, tetralin, fluorene and the like, univalent radicals. As univalent radicals, the aforementioned ring examples are named, phenyl, naphthyl, indanyl, tetralinyl, and fluorenyl.

[0056] "Arylene" generically refers to any aryl that has at least two groups attached thereto. For a more specific example, "phenylene" refers to a divalent phenyl ring radical. A phenylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0057] "Arylalkyl" refers to a residue in which an aryl moiety is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include benzyl, phenethyl, phenylvinyl, phenylallyl and the like. Both the aryl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of an arylalkyl group may be optionally substituted. "Lower arylalkyl" refers to an arylalkyl where the "alkyl" portion of the group has one to six carbons; this can also be refered to as C_{1-6} arylalkyl.

[0058] "Exo-alkenyl" refers to a double bond that emanates from an annular carbon, and is not within the ring system, for example the double bond depicted in the formula below.



[0059] In some examples, as appreciated by one of ordinary skill in the art, two adjacent groups on an aromatic system may be fused together to form a ring structure. The fused ring structure may contain heteroatoms and may be optionally substituted with one or more groups. It should additionally be noted that saturated carbons of such fused groups (i.e. saturated ring structures) can contain two substitution groups.

[0060] "Fused-polycyclic" or "fused ring system" refers to a polycyclic ring system that contains bridged or fused rings; that is, where two rings have more than one shared atom in their ring structures. In this application, fused-polycyclics and fused ring systems are not necessarily all aromatic ring systems. Typically, but not necessarily, fused-polycyclics share a vicinal set of atoms, for example naphthalene or 1,2,3,4-tetrahydro-naphthalene. A spiro ring system is not a fused-polycyclic by this definition, but fused polycyclic ring systems of the invention may themselves have spiro rings attached thereto via a single ring atom of the fused-polycyclic.

[0061] "Halogen" or "halo" refers to fluorine, chlorine, bromine or iodine. "Haloalkyl" and "haloaryl" refer generically to alkyl and aryl radicals that are substituted with one or more halogens, respectively. Thus, "dihaloaryl," "dihaloalkyl," "trihaloaryl" etc. refer to aryl and alkyl substituted with a plurality of halogens, but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl.

[0062] "Heteroarylene" generically refers to any heteroaryl that has at least two groups attached thereto. For a more specific example, "pyridylene" refers to a divalent pyridyl ring radical. A pyridylene, thus may have more than two groups attached, but is defined by a minimum of two non-hydrogen groups attached thereto.

[0063] "Heteroatom" refers to O, S, N, or P.

[0064] "Heterocyclyl" refers to a stable three- to fifteen-membered ring radical that consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems as well as spirocyclic systems; and the nitrogen, phosphorus, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized to various oxidation states. In a specific example, the group $-S(O)_{0-2}-$, refers to -S- (sulfide), -S(O)- (sulfoxide), and $-SO_2-$ (sulfone). For convenience, nitrogens, particularly but not exclusively, those defined as annular aromatic nitrogens, are meant to include their corresponding *N*-oxide form, although not explicitly defined as such in a particular example. Thus, for a compound of the invention having, for example, a pyridyl ring; the corresponding pyridyl-*N*-oxide is meant to be included as another compound of the invention. In addition, annular nitrogen atoms may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of heterocyclyl radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl,

benzodioxanyl, benzofuranyl, carbazoyl, cinnolinyl, diazepanyl, 1,4-diazepanyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, dihydropyridinyl, tetrahydropyridinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxazolidinyl, triazolyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothieliyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, dioxaphospholanyl, and oxadiazolyl.

[0065] "Heteroalicyclic" refers specifically to a non-aromatic heterocyclyl radical. A heteroalicyclic may contain unsaturation, but is not aromatic.

[0066] "Heteroaryl" refers specifically to an aromatic heterocyclyl radical.

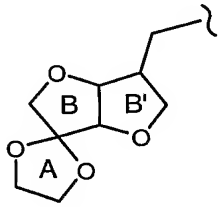
[0067] "Heterocyclylalkyl" refers to a residue in which a heterocyclyl is attached to a parent structure via one of an alkylene, alkylidene, or alkylidyne radical. Examples include (4-methylpiperazin-1-yl) methyl, (morpholin-4-yl) methyl, (pyridine-4-yl) methyl, 2-(oxazolin-2-yl) ethyl, 4-(4-methylpiperazin-1-yl)-2-butenyl, and the like. Both the heterocyclyl, and the corresponding alkylene, alkylidene, or alkylidyne radical portion of a heterocyclylalkyl group may be optionally substituted. "Lower heterocyclylalkyl" refers to a heterocyclylalkyl where the "alkyl" portion of the group has one to six carbons. "Heteroalicyclylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is non-aromatic; and "heteroarylalkyl" refers specifically to a heterocyclylalkyl where the heterocyclyl portion of the group is aromatic Such terms may be described in more than one way, for example, "lower heterocyclylalkyl" and "heterocyclyl C_{1-6}alkyl" are equivalent terms.

[0068] "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. One of ordinary skill in the art would understand that, with respect to any molecule described as

containing one or more optional substituents, that only sterically practical and/or synthetically feasible compounds are meant to be included. "Optionally substituted" refers to all subsequent modifiers in a term, for example in the term "optionally substituted arylC_{1-8}alkyl," optional substitution may occur on both the "C_{1-8}alkyl" portion and the "aryl" portion of the molecule; and for example, optionally substituted alkyl includes optionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially *ad infinitum*. A list of exemplary optional substitutions is included below in the definition of "substituted."

[0069] "Saturated bridged ring system" refers to a bicyclic or polycyclic ring system that is not aromatic. Such a system may contain isolated or conjugated unsaturation, but not aromatic or heteroaromatic rings in its core structure (but may have aromatic substitution thereon). For example, hexahydro-furo[3,2-b]furan, 2,3,3a,4,7,7a-hexahydro-1H-indene, 7-aza-bicyclo[2.2.1]heptane, and 1,2,3,4,4a,5,8,8a-octahydro-naphthalene are all included in the class "saturated bridged ring system.

[0070] "Spirocyclyl" or "spirocyclic ring" refers to a ring originating from a particular annular carbon of another ring. For example, as depicted below, a ring atom of a saturated bridged ring system (rings B and B'), but not a bridgehead atom, can be a shared atom between the saturated bridged ring system and a spirocyclyl (ring A) attached thereto. A spirocyclyl can be carbocyclic or heteroalicyclic.



[0071] "Substituted" alkyl, aryl, and heterocyclyl, refer respectively to alkyl, aryl, and heterocyclyl, wherein one or more (for example up to about five, in another example, up to about three) hydrogen atoms are replaced by a substituent independently selected from: optionally substituted alkyl (for example, fluoromethyl, hydroxypropyl, nitromethyl, aminoethyl and the like.), optionally substituted aryl (for example, 4-hydroxyphenyl, 2,3-difluorophenyl, and the like), optionally substituted arylalkyl (for example, 1-phenyl-ethyl, *para*-methoxyphenylethyl and the like), optionally substituted heterocyclylalkyl (for example, 1-pyridin-3-yl-ethyl, N-ethylmorphonlino and the like), optionally substituted heterocyclyl (for example, 5-chloro-pyridin-3-yl, 1-methyl-piperidin-4-yl and the like), optionally substituted alkoxy (for example methoxyethoxy, hydroxypropyloxy,

methylenedioxy and the like), optionally substituted amino (for example, methylamino, diethylamino, trifluoroacetylamino and the like), optionally substituted amidino, optionally substituted aryloxy (for example, phenoxy, *para*-chlorophenoxy, *meta*-aminophenoxy, *para*-phenoxyphenoxy and the like), optionally substituted arylalkyloxy (for example, benzyloxy, 3-chlorobenzyloxy, *meta*-phenoxybenzyloxy and the like), carboxy (-CO_2H), optionally substituted carboalkoxy (that is, acyloxy or -OC(=O)R), optionally substituted carboxyalkyl (that is, esters or -CO_2R), optionally substituted carboxamido, optionally substituted benzyloxycarbonylamino (CBZ-amino), cyano, optionally substituted acyl, halogen, hydroxy, nitro, optionally substituted alkylsulfanyl, optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, thiol, halogen, hydroxy, oxo, carbamyl, optionally substituted acylamino, optionally substituted hydrazino, optionally substituted hydroxylamino, and optionally substituted sulfonamido.

[0072] "Sulfanyl" refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), and -S-(optionally substituted heterocyclyl).

[0073] "Sulfinyl" refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-optionally substituted aryl), and -S(O)-(optionally substituted heterocyclyl).

[0074] "Sulfonyl" refers to the groups: -$S(O_2)$-H, -$S(O_2)$-(optionally substituted alkyl), -$S(O_2)$-optionally substituted aryl), -$S(O_2)$-(optionally substituted heterocyclyl), -$S(O_2)$-(optionally substituted alkoxy), -$S(O_2)$-optionally substituted aryloxy), and -$S(O_2)$-(optionally substituted heterocyclyloxy).

[0075] Some of the compounds of the invention may have imino, amino, oxo or hydroxy substituents off aromatic heterocyclyl systems. For purposes of this disclosure, it is understood that such imino, amino, oxo or hydroxy substituents may exist in their corresponding tautomeric form, i.e., amino, imino, hydroxy or oxo, respectively.

[0076] Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS).

[0077] The compounds of the invention, or their salts, may have asymmetric carbon atoms, oxidized sulfur atoms or quaternized nitrogen atoms in their structure.

[0078] The compounds of the invention and their salts may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also

exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0079] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0080] It is assumed that when considering generic descriptions of compounds of the invention for the purpose of constructing a compound, such construction results in the creation of a stable structure. That is, one of ordinary skill in the art would recognize that there can theoretically be some constructs which would not normally be considered as stable compounds (that is, sterically practical and/or synthetically feasible, *supra*).

[0081] When a particular group with its bonding structure is denoted as being bonded to two partners; that is, a divalent radical, for example, $-OCH_2-$, then it is understood that either of the two partners may be bound to the particular group at one end, and the other partner is necessarily bound to the other end of the particular group, unless stated explicitly otherwise. Stated another way, divalent radicals are not to be construed as limited to the depicted orientation, for example "$-OCH_2-$" is meant to mean not only "$-OCH_2-$" as drawn, but also "$-CH_2O-$."

[0082] "Subject" for the purposes of the present invention includes plants, humans and other animals, particularly mammals and other organisms, and home and garden materials (such as wood-based products subject to deterioation by termites). Thus the methods are applicable to agricultural, human therapy and veterinary, and home and garden applications. In a preferred embodiment the subject is a plant.

[0083] "Effective amount" is an amount of a compound of the invention, that when administered to a subject adversely affects the viability of the subject, e.g., that kill, paralyze, sterilize or otherwise disable pest species. The amount of a compound of the invention which constitutes an "effective amount" will vary depending on the compound, the subject's state and its severity, the age of the subject to be treated, and the like. The effective amount can be determined routinely by one of ordinary skill in the art having regard to his/her own knowledge and to this disclosure.

[0084] "Control pests" or "controlling pest" as used herein refers generally to use of the compounds and compositions to adversely affect pest viability, e.g., that kill, paralyze,

sterilize or otherwise disable pest species in the areas of agricultural crop protection, human and animal health.

[0085] "Administering to" as used herein covers many forms and ways of administering the compounds or compositions of the present invention to subjects. Administering to subjects includes, but is not limited to direct administration to subjects as well as indirect administration. Administration can be done prophylactically or therapeutically.

[0086] "Pests" as used herein refers generally to species that include insects, arachnids, helminths and mollusks, and other parasites and disease vectors, very especially preferably for controlling insects and arachnids, which are encountered in agriculture, in livestock breeding, in forests, in the protection of stored goods and materials (home and garden applications) and in the hygiene sector, and have good plant tolerance and favorable toxicity to warm-blooded species. They are active against normally sensitive and resistant species and against all or individual development stages.

[0087] The abovementioned pests include: From the order of the Acarina, for example, Acarus siro, Argas spp., Ornithodoros spp., Dermanyssus gallinae, Eriophyes ribis, Phyllocoptruta oleivora, Boophilus spp., Rhipicephalus spp., Amblyomma spp., Hyalomma spp., Ixodes spp., Psoroptes spp., Chorioptes spp., Sarcoptes spp., Tarsonemus spp., Bryobia praetiosa, Panonychus spp., Tetranychus spp., Eotetranychus spp., Oligonychus spp. And Eutetranychus spp. From the order of the Isopoda, for example, Oniscus asselus, Armadium vulgare and Porcellio scaber. From the order of the Diplopoda, for example, Blaniulus guttulatus. From the order of the Chilopoda, for example, Geophilus carpophagus and Scutigera spp. From the order of the Symphyla, for example, Scutigerella immaculata. From the order of the Thysanura, for example, Lepisma saccharina. From the order of the Collembola, for example, Onychiurus armatus. From the order of the Orthoptera, for example, Blatta orientalis, Periplaneta americana, Leucophaea madeira, Blattella germanica, Acheta domesticus, Gryllotalpa spp., Locusta migratoria migratorioides, Melanoplus differentialis and Schistocerca gregaria. From the order of the Isoptera, for example, Reticulitermes spp. From the order of the Anoplura, for example, Phylloera vastatrix, Pemphigus spp., Pediculus humanus corporis, Haematopinus spp. and Linognathus spp. From the order of the Mallophaga, for example, Trichodectes spp. and Damalinea spp. From the order of the Thysanoptera, for example, Hercinothrips femoralis and Thrips tabaci. From the order of the Heteroptera, for example, Eurygaster spp., Dysdercus intermedius, Piesma quadrata, Cimex lectularius,

Rhodnius prolixus and Triatoma spp. From the order of the Homoptera, for example, Aleurodes brassicae, Bemisia tabaci, Trialeurodes vaporariorum, Aphis gossypii, Brevicoryne brassicae, Cryptomyzus ribis, Doralis fabae, Doralis pomi, Eriosoma lanigerum, Hyalopterus arundinis, Macrosiphum avenae, Myzus spp., Phorodon humuli, Rhopalosiphum padi, Empoasca spp., Euscelus bilobatus, Nephotettix cincticeps, Lecanium corni, Saissetia oleae, Laodelphax striatellus, Nilaparvata lugens, Aonidiella aurantii, Aspidiotus hederae, Pseudococcus spp. and Psylla spp. From the order of the Lepidoptera, for example, Pectinophora gossypiella, Bupalus piniarius, Cheimatobia brumata, Lithocolletis blancardella, Hyponomeuta padella, Plutella maculipennis, Malacosoma neustria, Euproctis chrysorrhoea, Lymantria spp., Bucculatrix thurberiella, Phyllocnistis citrella, Agrotis spp., Euxoa spp., Feltia spp., Earias insulana, Heliothis spp., Laphygma exigua, Mamestra brassicae, Panolis flammea, Prodenia litura, Spodoptera spp., Trichoplusia ni, Carpocapsa pomonella, Pieris spp., Chilo spp., Pyrausta nubilalis, Ephestia kuehniella, Galleria mellonella, Cacoecia podana, Capua reticulana, Choristoneura fumiferana, Clysia ambiguella, Homona magnanima and Tortrix viridana. From the order of the Coleoptera, for example, Anobium punctatum, Rhizopertha dominica, Bruchidius obtectus, Acanthoscelides obtectus, Hylotrupes bajulus, Agelastica alni, Leptinotarsa decemlineata, Phaedon cochleariae, Diabrotica spp., Psylloides chrysocephala, Epilachna varivestis, Atomaria spp., Oryzaephilus surinamensis, Anthonumus spp., Sitophilus spp., Otiorrhynchus sulcatus, Cosmopolites sordidus, Ceuthorrynchus assimilis, Hypera postica, Dermestes spp., Trogoderma, Anthrenus spp., Attagenus spp., Lyctus spp., Meligethes aeneus, Ptinus spp., Niptus hololeucus, Gibbium psylloides, Tribolium spp., Tenebrio molitor, Agriotes spp., Conoderus spp., Melolontha melolontha, Amphimallon solstitialis and Costelytra zealandica. From the order of the Hymenoptera, for example, Diprion spp., Hoplocampa spp., Lasius spp., Monomorium pharaonis and Vespa spp. From the order of the Diptera, for example, Aedes spp., Anopheles spp., Culex spp., Drosophila melanogaster, Musca spp., Fannia spp., Calliphora erythiocephala, Lucilia spp., Chrysomyia spp., Cuterebra spp., Gastrophilus spp., Hypobosca spp., Stomoxys spp., Oestrus spp., Hypoderma spp., Tabanus spp., Tannia spp., Bibio hortulanus, Oscinella frit, Phorbia spp., Pegomyia hyoscyami, Ceratitis capitata, Dacus oleae and Tipula paludosa. From the order of the Siphonaptera, for example, Xenopsylla cheopsis and Ceratophyllus spp. From the order of the Arachnida, for example, Scorpio maurus and Latrodectus mactans. From the class of helminths, for example, Haemonchus, Trichostrongulus, Ostertagia, Cooperia, Chabertia, Strongyloides,

Oesophagostomum, Hyostrongulus, Ancylostoma, Ascaris and Heterakis, as well as Fasciola. From the class of the Gastropoda, for example, Deroceras spp., Arion spp., Lymnaea spp., Galba spp., Succinea spp., Biomphalaria spp., Bulinus spp. and Oncomelania spp. From the class of Bivalva, for example, Dreissena spp.

[0088] The phytoparasitic nematodes which can be controlled according to the invention include, for example, the root-parasitic soil nematodes, such as, for example, those of the genera Meloidogyne (root gall nematodes, such as Meloidogyne incognita, Meloidogyne hapla and Meloidogyne javanica), Heterodera and Globodera (cyst-forming nematodes, such as Globodera rostochiensis, Globodera pallida and Heterodera trifolii) and of the genera Radopholus, such as Radopholus similis, Pratylenchus, such as Pratylenchus neglectus, Pratylenchus penetrans and Pratylenchus curvitatus; Tylenchulus, such as Tylenchulus semipenetrans, Tylenchorhynchus, such as Tylenchorhynchus dubius and Tylenchorhynchus claytoni, Rotylenchus, such as Rotylencus robustus, Heliocotylenchus, such as Heliocotylenchus multicinctus, Belonoaimus, such as Belonoaimus longicaudatus, Longidorus, such as Longidorus elongatus, Trichodorus, such as Trichodorus primitivus and Xiphinema, such as Xiphinema index.

[0089] The nematode genera Ditylenchus (stem parasites, such as Ditylenchus dipsaci and Ditylenchus destructor), Aphelenchoides (leaf nematodes, such as Aphelenchoides ritzemabosi) and Anguina (blossom nematodes, such as Anguina tritici) can furthermore be controlled with the compounds according to the invention.

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[0090] The compositions of the present invention may comprise at least one compound of Formula I as well as suitable formulation auxiliaries. In general, the compositions according to the invention comprise from 1 to 95% by weight of the active compounds of the Formula I. The compositions can be formulated in various ways, depending on how this is determined by the biological and/or chemico-physical parameters. Suitable formulation possibilities are therefore: wettable powders (WP), emulsifiable concentrates (EC), aqueous solutions (SL), emulsions, sprayable solutions, oil- or water-based dispersions (SC), suspoemulsions (SE), dusting powders (DP), seed dressings, granules in the form of microgranules, sprayed granules, absorption granules and adsorption

granules, water-dispersible granules (WG), ULV formulations, microcapsules, waxes or baits.

[0091] These individual types of formulation are known in principle and are described, for example, in: Winnacker-Kuchler, "Chemische Technologie" [Chemical Technology], Volume 7, C. Hauser Verlag Munich, 4th Edition 1986; van Falkenberg, "Pesticides Formulations", Marcel Dekker N.Y., 2nd Edition 1972-73; K. Martens, "Spray Drying Handbook", 3rd Edition 1979, G. Goodwin Ltd. London.

[0092] The necessary formulation auxiliaries, i.e. carrier substances and/or surface-active substances, such as inert materials, surfactants, solvents and further additives, are likewise known and are described, for example, in: Watkins, "Handbook of Insecticide Dust Diluents and Carriers", 2nd Edition, Darland Books, Caldwell N.J.; H. v. Olphen, "Introduction to Clay Colloid Chemistry", 2nd Edition, J. Wiley & Sons, N.Y.; Marsden, "Solvents Guide", 2nd Edition, Interscience, N.Y. 1950; McCutcheon's, "Detergents and Emulsifiers Annual", MC Publ. Corp., Ridgewood N.J.; Sisley and Wood, "Encyclopedia of Surface Active Agents", Chem. Publ. Co. Inc., N.Y. 1964; Schonfeldt, "Grenzflachenaktive Athylenoxidaddukte" [Surface-active ethylene oxide adducts], Wiss. Verlagsgesell., Stuttgart 1967; Winnacker-Kuchler, "Chemische Technologie" [Chemical Technology], Volume 7, C. Hauser Verlag Munich, 4th Edition 1986.

[0093] Combinations with other substances having a pesticidal action, fertilizers and/or growth regulators can be prepared on the basis of these formulations, for example in the form of a ready-to-use formulation or as a tank mix. Wettable powders are preparations which are uniformly dispersible in water and which, alongside the active compound, and in addition to a diluent or inert substance, also comprise wetting agents, for example polyethoxylated alkylphenols, polyethoxylated fatty alcohols or alkyl- or alkylphenolsulfonates, and dispersing agents, for example sodium ligninsulfonate or sodium 2,2'-dinaphthylmethane-6,6'-disulfonate. Emulsifiable concentrates are prepared by dissolving the active compound in an organic solvent, for example butanol, cyclohexanone, dimethylformamide, xylene or also higher-boiling aromatics or hydrocarbons, with the addition of one or more emulsifiers.

[0094] Emulsifiers which can be used are, for example: calcium alkylarylsulfonates, such as Ca dodecylbenzenesulfonate, or nonionic emulsifiers, such as fatty acid polyglycol esters, alkylaryl polyglycol ethers, fatty alcohol polyglycol ethers, propylene

oxide/ethylene oxide condensation products, alkyl polyethers, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters or polyoxyethylene sorbitol esters.

[0095] Dusting powders are obtained by grinding the active compound with finely divided solid substances, for example talc, naturally occurring clays, such as kaolin, bentonite and pyrophillite, or diatomaceous earth. Granules can be prepared either by spraying the active compound onto granular inert material capable of adsorption or by applying active compound concentrates to the surface of carrier substances, such as sand, kaolinites or granular inert material, by means of adhesives, for example polyvinyl alcohol, sodium polyacrylate or mineral oils. Suitable active compounds can also be granulated in the manner customary for the preparation of fertilizer granules--if desired as a mixture with fertilizers.

[0096] In wettable powders, the active compound concentration is generally about 10 to 90% by weight, the remainder to make up 100% by weight comprising customary formulation constituents. In emulsifiable concentrates, the active compound concentration can be about 5 to 80% by weight. Dust-like formulations usually comprise 5 to 20% by weight of active compound, and sprayable solutions about 2 to 20% by weight. In granules, the content of active compound partly depends on whether the active compound is present in liquid or solid form and what granulating auxiliaries, fillers and the like are used.

[0097] In addition, the active compound formulations mentioned comprise, if appropriate, the particular customary tackifiers, wetting agents, dispersing agents, emulsifiers, penetration agents, solvents, fillers or carrier substances.

[0098] For use, the concentrates in the commercially available form are diluted in the customary manner, if appropriate, for example by means of water in the case of wettable powders, emulsifiable concentrates, dispersions and in some cases also microgranules. Dust-like and granular formulations as well as sprayable solutions are usually not diluted further with additional inert substances before use.

[0099] The required amount applied varies with the external conditions, such as temperature, humidity and the like. It can vary within wide limits, for example between 0.0005 and 10.0 kg/ha or more of active substance, but is preferably between 0.001 and 5 kg/ha of active compound.

[0100] The active compounds according to the invention can be present in their commercially available formulations and in the use forms prepared from these formulations as mixtures with other active compounds, such as insecticides, attractants, sterilizing agents, acaricides, nematicides, fungicides, growth-regulating substances or herbicides.

[0101] The pesticides include, for example, phosphoric acid esters, carbamates, carboxylic acid esters, formamidines, tin compounds and substances produced by microorganisms. Preferred partners for the mixtures are: 1. from the group of phosphorus compounds acephate, azamethiphos, azinphos-ethyl, azinphos-methyl, bromophos, bromophos-ethyl, cadusafos (F-67825), chlorethoxyphos, chlorfenvinphos, chlormephos, chlorpyrifos, chlorpyrifos-methyl, demeton, demeton-S-methyl, demeton-S-methyl sulfone, dialifos, diazinon, dichlorvos, dicrotophos, dimethoate, disulfoton, EPN, ethion, ethoprophos, etrimfos, famphur, fenamiphos, fenitriothion, fensulfothion, fenthion, fonofos, formothion, fosthiazate (ASC-66824), heptenophos, isazophos, isothioate, isoxathion, malathion, methacrifos, methamidophos, methidathion, salithion, mevinphos, monocrotophos, naled, omethoate, oxydemeton-methyl, parathion, parathion-methyl, phenthoate, phorate, phosalone, phosfolan, phosphocarb (BAS-301), phosmet, phosphamidon, phoxim, pirimiphos, primiphos-ethyl, pirimiphos-methyl, pro fenofos, propaphos, proetamphos, prothiofos, pyraclofos, pyridapenthion, quinaiphos, sulprofos, temephos, terbufos, tebupirimfos, tetrachlorvinphos, thiometon, triazophos, trichlorphon, vamidothion; 2. from the group of carbamates alanycarb (OK-135), aldicarb, 2-sec-butylphenyl methylcarbamate (BPMC), carbaryl, carbofliran, carbosulfan, cloethocarb, benfuiracarb, ethiofencarb, furathiocarb, HCN-801, isoprocarb, methomyl, 5-methyl-m-cumenyl butyryl(methyl)carbamate, oxamyl, pirimicarb, propoxur, thiodicarb, thiofanox, 1-methylthio(ethylideneamino) N-methyl-N-(morpholinothio)carbamate (UC 51717), triazamate; 3. from the group of carboxylic acid esters acrinathrin, allethrin, alphametrin, 5-benzyl-3-furyl methyl (E)-(1R)-cis-2,2-di-methyl-3-(2-oxothiolan-3-ylidenemethyl)cyclo-propanecar boxylate, beta-cyfluthrin, beta-cypermethrin, bioallethrin, bioallethrin ((S)-cyclopentyl isomer), bioresmethrin, bifenthrin, (RS)-1-cyano-1-(6-phenoxy-2-pyridyl)methyl (1RS)-trans-3-(4-tert-butylphenyl)-2,2-dimethylcyclopropanecarboxylate (NCI 85193), cycloprothrin, cyfluthrin, cyhalothrin, cythithrin, cypermethrin, cyphenothrin, deltamethrin, empenthrin, esfenvalerate, fenfluthrin, fenpropathrin, fenvalerate, flucythrinate, flumethrin, fluvalinate (D isomer), imiprothrin (S-41311), lambda-cyhalothrin, permethrin, pheothrin ((R) isomer),

prallethrin, pyrethrins (natural products), resmethrin, tefluthrin, tetramethrin, theta-cypermethrin (TD-2344), tralomethrin, transfluthrin and zeta-cypermethrin (F-56701); 4. from the group of amidines amitraz, chlordimeform; 5. from the group of tin compounds cyhexatin, fenbutatin oxide; 6. others abamectin, ABG-9008, acetamiprid, Anagrapha falcitera, AKD-1022, AKD-3059, ANS-118, Bacillus thuringiensis, Beauveria bassianea, bensultap, bifenazate (D-2341), binapacryl, BJL-932, bromopropylate, BTG-504, BTG-505, buprofezin, camphechlor, cartap, chlorobenzilate, chlorfenapyr, chlorfluazuron, 2-(4-chlorophenyl)-4,5-diphenylthiophene (UBI-T 930), chlorfentezine, chromafenozide (ANS-118), CG-216, CG-217, CG-234, A-184699, 2-naphthylmethyl cyclopropanecarboxylate (Ro 12-0470), cyromazin, diacloden (thiamethoxam), diafenthiuron, N-(3,5-dichloro-4-(1,1,2,3,3,3-hexafluoro-1-propyloxy)phenyl)carbamoyl)-2- chlorobenzocarboxamide acid ethyl ester, DDT, dicofol, diflubenzuron, N-(2,3-dihydro-3-methyl-1,3-thiazol-2-ylidene)-2,4-xylidine, dinobuton, dinocap, diofenolan, DPX-062, emamectin-benzoate (MK-244), endosulfan, ethiprole (sulfethiprole), ethofenprox, etoxazole (YI-5301), fenazaquin, fenoxycarb, fipronil, fluazuron, flumite (flufenzine, SZI-121), 2-fluoro-5-(4-(4-ethoxyphenyl)-4-methyl-1-pentyl)diphenyl ether (MTI 800), granulosis and nuclear polyhedrosis viruses, fenpyroximate, fenthiocarb, flubenzimine, flucycloxuron, flufenoxuron, flufenprox (ICI-A5683), fluproxyfen, gamma-HCH, halofenozide (RH-0345), halofenprox (MTI-732), hexaflumuron (DE.sub.-- 473), hexythiazox, HOI-9004, hydramethylnon (AC 217300), lufenuron, imidacloprid, indoxacarb (DPX-MP062), kanemite (AKD-2023), M-020, MTI-446, ivermectin, M-020, methoxyfenozide (Intrepid, RH-2485), milbemectin, NC-196, neemgard, nitenpyram (TI-304), 2-nitromethyl-4,5-dihydro-6H-thiazine (DS 52618), 2-nitromethyl-3,4-dihydrothiazole (SD 35651), 2-nitromethylene-1,2-thiazinan-3-ylcarbamaldehyde (WL 108477), pyriproxyfen (S-71639), NC-196, NC-1111, NNI-9768, novaluron (MCW-275), OK-9701, OK-9601, OK-9602, propargite, pymethrozine, pyridaben, pyrimidifen (SU-8801), RH-0345, RH-2485, RYI-210, S-1283, S-1833, SB7242, SI-8601, silafluofen, silomadine (CG-177), spinosad, SU-9118, tebufenozide, tebufenpyrad (MK-239), teflubenzuron, tetradifon, tetrasul, thiacloprid, thiocyclam, TI-435, tolfenpyrad (OMI-88), triazamate (RH-7988), triflumuron, verbutin, vertalec (Mykotal), YI-5301.

[0102] The abovementioned combination partners are known active compounds, and most of them are described in Ch. R. Worthing, S. B. Walker, The ***Pesticide*** Manual, 11th Edition, British Crop Protection Council Farnham 1997.

[0103] The active compound content of the use forms prepared from the commercially available formulations can be from 0.00000001 to 95% by weight of active compound, preferably between 0.00001 and 1% by weight. The active compounds are used in a customary manner appropriate for the use forms.

[0104] The active compounds of the Formula I according to the invention also have excellent systemic action and can be used in the agricultural field. The active compounds can therefore also be introduced into the plants via below-ground and above-ground parts of plants (root, stem, leaf), when the active compounds are applied in liquid or solid form to the immediate surroundings of the plants (for example granules in soil application, application in flooded rice fields).

[0105] Furthermore, the active compounds according to the invention are particularly useful for treating vegetative and generatative propagation stock, such as, for example, seed of, for example, cereals, vegetables, cotton, rice, sugar beet and other crops and ornamentals, of bulbs, cuttings and tubers of other vegetatively propagated crops and ornamentals. To this end, treatment can be carried out prior to sowing or planting (for example by special seed coating techniques, by seed dressings in liquid or solid form or by seed box treatment), during sowing or planting or after sowing or planting by special application techniques (for example seed row treatment). Depending on the application, the amount of active compound applied can vary within a relatively wide range. In general, the application rates are between 1 g and 10 kg of active compound per hectare of soil area.

[0106] The compounds of the Formula I can also be used for controlling harmful plants in crops of known genetically modified plants or of genetically modified plants still to be developed. The transgenic plants generally have particularly advantageous properties, for example resistance to certain crop protection agents, resistance to plant diseases or pathogens of plant diseases, such as certain insects or microorganisms, such as fungi, bacteria or viruses. Other special properties relate, for example, to the harvested product, with respect to quantity, quality, shelf-life, composition and special ingredients. Thus, transgenic plants having increased starch content or a modified quality of the starch or those having a different fatty acid composition of the harvested product are known.

[0107] Preference is given to the use in economically important transgenic crops of useful and ornamental plants, for example cereals, such as wheat, barley, rye, oats, millet, rice,

manioc and maize, or else crops of sugar beet, cotton, soya, rapeseed, potato, tomato, pea and other vegetable species.

[0108] The use in transgenic crops, in particular crops with resistance to insects, is, in addition to the effects with respect to harmful organisms which can be observed in other crops, frequently associated with effects which are specific for the application in the respective transgenic crop, for example a modified or specifically widened spectrum of pests which can be controlled, or modified application rates which can be used for the application.

[0109] The use of the compounds according to the invention comprises, in addition to direct application to the pests, any other application where the compounds of the Formula I act on the pests. Such indirect applications may be, for example, the use of compounds which decompose or are degraded to compounds of the Formula I, for example in the soil, the plant or the pest.

[0110] The active compounds according to the invention are also suitable for controlling endo- and ectoparasites in the veterinary medicine field and in the field of animal husbandry. The active compounds according to the invention are used here in a known manner, such as by oral use in the form of, for example, tablets, capsules, potions or granules, by means of dermal use in the form of, for example, dipping, spraying, pouring-on, spotting-on and dusting, and by parenteral use in the form of, for example, injection.

[0111] The novel compounds of the Formula I can accordingly also particularly advantageously be used in livestock husbandry (for example cattle,. sheep, pigs and poultry, such as chickens, geese and the like). In a preferred embodiment of the invention, the compounds are administered orally to the animals, if appropriate in suitable formulations and if appropriate with the drinking water or feed. Since excretion in the feces takes place in an active manner, the development of insects in the feces of the animals can be prevented very easily in this way. The dosages and formulations suitable in each case depend in particular on the species and the development stage of the stock animals and also on the level of infestation, and can easily be determined and specified by the customary methods. The compounds can be employed in cattle, for example, in dosages of 0.01 to 1 mg/kg of body weight.

[0112] The examples below serve to illustrate the invention.

Abbreviations and their Definitions

[0113] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	Acetyl
CAN	Acetonitrile
ATP	adenosine triphosphate
BNB	4-bromomethyl-3-nitrobenzoic acid
Boc	t-butyloxy carbonyl
Br	Broad
Bu	Butyl
°C	degrees Celsius
c-	Cyclo
CBZ	CarboBenZoxy = benzyloxycarbonyl
D	Doublet
Dd	doublet of doublet
Dt	doublet of triplet
DBU	Diazabicyclo[5.4.0]undec-7-ere
DCM	dichloromethane = methylene chloride = CH_2Cl_2
DCE	Dichloroethylene
DEAD	diethyl azodicarboxylate
DIC	Diisopropylcarbodiimide
DIEA	N,N-diisopropylethyl amine
DMAP	4-N,N-dimethylaminopyridine
DMF	N,N-dimethylfonnamide
DMSO	dimethyl sulfoxide
DVB	1,4-divinylbenzene
EEDQ	2-ethoxy-l-ethoxycarbonyl-1,2-dihydroquinoline
EI	Electron Impact ionization
Et	Ethyl
Fmoc	9-fluorenylmethoxycarbonyl
G	gram(s)
GC	gas chromatography

Abbreviation	Meaning
H or hr	hour(s)
HATU	0-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	Hexamethyldisilazane
HOAc	acetic acid
HOBt	Hydroxybenzotriazole
HPLC	high pressure liquid chromatography
L	liter(s)
M	molar or molarity
M	Multiplet
Me	Methyl
mesyl	Methanesulfonyl
mg	milligram(s)
MHz	megahertz (frequency)
Min	minute(s)
mL	milliliter(s)
mM	Millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
MTBE	methyl t-butyl ether
N	normal or normality
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NM	Nanomolar
NMO	N-methylmorpholine oxide
NMR	nuclear magnetic resonance spectroscopy
PEG	polyethylene glycol
pEY	poly-glutamine, tyrosine
Ph	Phenyl
PhOH	Phenol

Abbreviation	Meaning
PfP	Pentafluorophenol
PfPy	Pentafluoropyridine
PPTS	Pyridinium p-toluenesulfonate
Py	Pyridine
PyBroP	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Q	Quartet
RT	Room temperature
Sat'd	Saturated
S	Singlet
S-	Secondary
T-	Tertiary
T or tr	Triplet
TBDMS	t-butyldimethylsilyl
TES	Triethylsilane
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TMOF	trimethyl orthoformate
TMS	Trimethylsilyl
tosyl	p-toluenesulfonyl
Trt	Triphenylmethyl
μL	microliter(s)
μM	Micromole(s) or micromolar

Formulation Examples

[0114] a) A dusting powder is obtained by mixing 10 parts by weight of active compound and 90 parts by weight of talc, as inert substance, and comminuting the mixture in an impact mill. b) A wettable powder which is readily dispersible in water is obtained by mixing 25 parts by weight of active compound, 65 parts by weight of kaolin-containing quartz, as the inert substance, 10 parts by weight of potassium ligninsulfonate and 1 part by weight of sodium oleoylmethyltaurinate, as wetting and dispersing agent, and grinding

the mixture in a pinned disk mill. c) A dispersion concentrate which is readily dispersible in water is prepared by mixing 40 parts by weight of active compound with 7 parts by weight of a sulfosuccinic monoester, 2 parts by weight of a sodium ligninsulfonate and 51 parts by weight of water and grinding the mixture to a fineness of below 5 microns in a grinding bead mill. d) An emulsifiable concentrate can be prepared from 15 parts by weight of active compound, 75 parts by weight of cyclohexane, as the solvent, and 10 parts by weight of ethoxylated nonylphenol (10 EO), as the emulsifier. e) Granules can be prepared from 2 to 15 parts by weight of active compound and an inert granule carrier material, such as attapulgite, pumice granules and/or quartz sand. A suspension of the wettable powder from Example b) having a solids content of 30% is expediently used, and this is sprayed onto the surface of attapulgite granules and the components are dried and mixed intimately. The weight content of the wettable powder is approximately 5% and that of the inert carrier material is approximately 95% of the finished granules.

Biochemical Assays

Ethanolamine Kinase Assay

[0115] Ethanolamine kinase (EK) activity is measured as ethanolamine-dependent ATP consumption following the kinase reaction using luciferase-luciferin-coupled chemiluminescence. Briefly the kinase reaction containing ATP, ethanolamine and recombinant *Heliothis virescens* EK was conducted and final ATP concentrations were determined by the luciferase-catalyzed chemiluminescence; ATP consumption is directly correlated with the kinase activity.

[0116] For EK, the reaction mixture (80 nM EK, 50 μM ATP and 250 μM ethanolamine) was incubated at ambient temperature for 1 hr in assay buffer (88 mM Tris-HCl, pH 8.0, 10 mM $MgCl_2$, 1 mM DTT, 0.05% Tween-20). Following the kinase reaction, an equal volume of luciferase-luciferin mix (Promega) was added and the chemiluminescence signal was measured using a Victor multipurpose plate reader (Perkin Elmer). Dose-response experiments were performed using ten different inhibitor concentrations in a 384-well microtiter plate. The IC_{50} value, defined as the compound concentration resulting in 50% inhibition of enzyme activity, was calculated using nonlinear regression analysis.

Ethanolamine Kinase Cloning and Protein Expression

[0117] The full-length (354 aa) *H. virescens* EK cDNA was cloned and expressed as a recombinant protein in *E. coli*. The full length cDNA was subcloned into pET30b+ with the predicted ORF encoding for the native protein. This expression plasmid was transformed into BL21(DE3)-CodonPlus-RIL strain (Stratagene). Optimal yields of soluble cytoplasmic enzyme were obtained using the following conditions: A 1000 ml LB culture containing 100 μg/ml kanamycin was induced at an OD_{600} of 0.6 with 1 mM IPTG for 20 hours at 28°C. EK was purified from the *E. coli* lysate column chromatography employing DEAE-Sephacel (Pharmacia) followed by Source Q (Pharmacia). SDS-PAGE and activity analysis confirmed the product to be of >80% purity. N-terminal amino acid sequencing was consistent with the predicted native *H. virescens* EK sequence after removal of the initiator methionine. Electrospray MS analysis was consistent with this result (measured 41104 Da, theoretical 41100 Da). MS/MS sequencing of tryptic fragments gave 17% coverage of the protein, confirming the identity of the protein as EK.

[0118] The tested compounds show inhibitory activity towards EK with IC_{50} values less than 10 μM. Example compounds are shown in Table 2 below.

Bioassays

[0119] Bioassays were conducted on several species of insects. Example methodology is a follows.

[0120] *Aedes aeygpti* neonate larvae: Between 20 and 30 *A. aegypti* neonates were added to test wells immediately prior to addition of compound or control. Different concentrations of compound or control were added and larvae were observed for mortality/moribundity at 6, 24, 48 and 72 hrs after treatment. An LD_{50} @ 72 hours of ~ 8μg/ml was determined for EXEL-6723. Treated animals showed acute loco-motor defects within 24 hours at compound concentrations ≥ 17 μg/ml consistent with a block in EK activity. At these concentrations, animals were uncoordinated, sluggish and longitudinally shrunken. In addition compound treatment inhibited molting to L2 larvae at concentrations ≥ 2 μg/ml.

[0121] Diet surface overlay bioassays: Assays were conducted on first instar larvae/neonates of 3 lepidopteran species (Heliothis virescens, Spodoptera frugiperda and Plutella xylostella). Test compounds or controls were added to 10 wells and 3 first instar larvae were placed in each well. Insects were reared at 28°C. Visual observation of

insect viability were carried out at 6, 24, 48 and 72 hours post addition of larvae to the well. Total number of viable larvae were recorded at each time point. In vivo activity (~ 30% mortality) was observed for EXEL-6723 at 48 hours against Spodoptera frugiperda in feeding assays. Additional bioassays yielded further evidence of insecticidal activity for this chemical series.

Structure Activity Relationships

[0120] Table 2 shows structure activity relationship data for selected compounds of the invention. Inhibition is indicated as IC_{50} with the following key: A = IC_{50} less than 1000 nM, B = IC_{50} greater than 1000 nM, but less than 2500 nM, C = IC_{50} greater than 2500 nM, but less than 5000 nM, and D = IC_{50} equal to, or greater than 5000 nM.

Table 2

Entry	Name	EK
1	7-fluoro-4-methyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	A
2	7-chloro-4-methyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	B
3	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-7-(methylthio)quinoline	B
4	7-chloro-4,8-dimethyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	C
5	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-7-(methyloxy)quinoline	D
6	7-chloro-4-methyl-2-(4-methylpiperazin-1-yl)quinoline	D
7	2-azepan-1-yl-4-methyl-7-(methyloxy)quinoline	D
8	2-(4-ethylpiperazin-1-yl)-4-methyl-7-(methyloxy)quinoline	D
9	4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	D
10	6,7-bis(methyloxy)-2-[4-(tetrahydrofuran-2-ylcarbonyl)-1,4-diazepan-1-yl]quinazolin-4-amine	D
11	6,7-bis(methyloxy)-2-piperazin-1-ylquinazolin-4-amine	D
12	4-methyl-2-(4-methylpiperazin-1-yl)quinoline	D
13	7-chloro-4-methyl-2-(4-methylpiperidin-1-yl)quinoline	D

Table 2

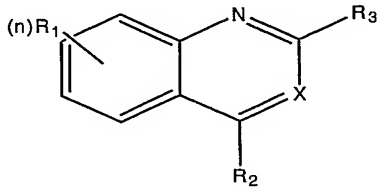
Entry	Name	EK
14	7-chloro-2-[4-(2,5-dimethylphenyl)piperazin-1-yl]-4-methylquinoline	D
15	2-azepan-1-yl-6-fluoro-4-methylquinoline	D
16	7-chloro-4-methyl-2-piperidin-1-ylquinoline	D
17	2-azepan-1-yl-7-chloro-4-methylquinoline	D
18	7-fluoro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	D
19	2-azepan-1-yl-4-methyl-8-(methyloxy)quinoline	D
20	7-chloro-4-methyl-2-(4-pyridin-2-ylpiperazin-1-yl)quinoline	D
21	2-[4-(3-chlorophenyl)piperazin-1-yl]-4-methyl-5,7-bis(methyloxy)quinoline	D
22	6-chloro-2-(4-ethylpiperazin-1-yl)-4-methylquinoline	D
23	2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methyl-7-(methyloxy)quinoline	D
24	7-fluoro-4-methyl-2-(4-pyridin-2-ylpiperazin-1-yl)quinoline	D
25	6-fluoro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	D
26	7-chloro-4-methyl-2-[4-(2-methylphenyl)piperazin-1-yl]quinoline	D
27	7-chloro-4-methyl-2-{4-[(2E)-3-phenylprop-2-en-1-yl]piperazin-1-yl}quinoline	D
28	2-azepan-1-yl-4-methyl-5,7-bis(methyloxy)quinoline	D
29	7-chloro-4-methyl-2-{4-[4-(methyloxy)phenyl]piperazin-1-yl}quinoline	D
30	7-chloro-4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	D
31	7-chloro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	D
32	7-fluoro-4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	D
33	7-chloro-4-methyl-2-(3-methylpiperidin-1-yl)quinoline	D
34	4-methyl-7-(methyloxy)-2-(4-phenylpiperazin-1-yl)quinoline	D
35	2-(4-acetylpiperazin-1-yl)-7-chloro-4-methylquinoline	D
36	7-chloro-2-[4-(4-chlorophenyl)piperazin-1-yl]-4-methylquinoline	D
37	7-chloro-2-[4-(3-chlorophenyl)piperazin-1-yl]-4-methylquinoline	D

Table 2

Entry	Name	EK
38	2-(4-ethylpiperazin-1-yl)-6-fluoro-4-methylquinoline	D
39	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-5,8-bis(methyloxy)quinoline	D
40	2-azocan-1-yl-7-chloro-4-methylquinoline	D
41	7-fluoro-4-methyl-2-(4-methylpiperazin-1-yl)quinoline	D
42	2-[4-(7-chloro-4-methylquinolin-2-yl)piperazin-1-yl]ethanol	D
43	4,8-dimethyl-2-(4-methylpiperazin-1-yl)quinoline	D
44	2-(4-methylpiperazin-1-yl)-4-morpholin-4-ylquinazoline	D

What is claimed is:

1. A composition for controlling pests, which comprises a carrier and an effective amount of at least one compound according to Formula **I**,



I

or an acceptable salt or hydrate thereof, wherein,

each of R^1 , R^2, R^3 are independently selected from -H, halogen, trihalomethyl, -CN, $-NO_2$, $-NH_2$, $-NR^5R^5$, $-S(O)_{0-2}R^5$, $-SO_2NR^5R^5$, $-CO_2R^5$, $-C(O)NR^5R^5$, $-N(R^5)SO_2R^5$, $-N(R^5)C(O)R^5$, $-N(R^5)CO_2R^5$, $-C(O)R^5$, optionally substituted lower alkyl, optionally substituted lower alkoxy, optionally substituted aryl, optionally substituted lower arylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, and optionally substituted arylalkyl;

X is CR^4 or N;

each of R^4 and R^5 are independently selected from H, optionally substituted C_{1-10}alkyl, optionally substituted C_{1-10}alkoxy, optionally substituted aryl, optionally substituted aryl-C_{1-10}alkyl, optionally substituted heterocyclyl, and optionally substituted heterocyclyl-C_{1-10}alkyl; and

n is an integer from 0-4.

2. The composition according to claim 1, wherein X is CR^4.

3. The composition according to claim 2, wherein X is CH.

4. The composition according to claim 3, wherein n is 1.

5. The composition according to claim 3, wherein n is 2.

6. The composition according to claim 4, wherein R^1 is halogen.

7. The composition according to claim 6, wherein R^1 is chlorine.

8. The composition according to claim 4, wherein R^1 is alkoxy.

9. The composition according to claim 4, wherein R^1 is methyl sulfate.

10. The composition according to claim 3, wherein R^2 is lower alkyl.

11. The composition according to claim 10, wherein R^2 is methyl.

12. The composition according to claim 3, wherein R^3 is optionally substituted heterocyclyl.

13. The composition according to claim 2, wherein R^3 is 1-methyl-[1, 4]diazepane.

14. The composition according to claim 1, wherein the compound is selected from Table 3.

Table 3

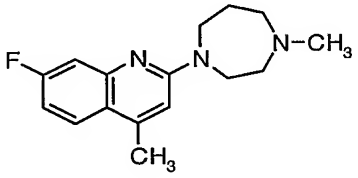
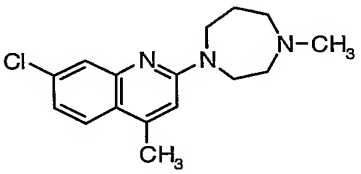
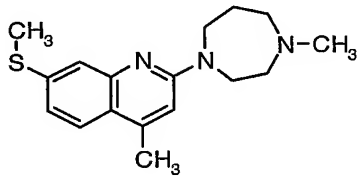
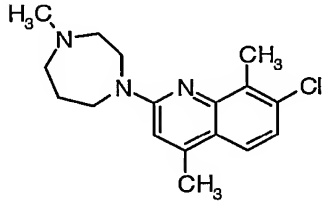
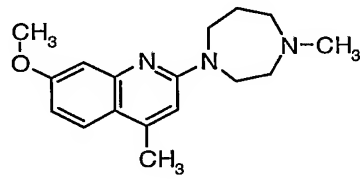
Entry	Name	Structure
1	7-fluoro-4-methyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	
2	7-chloro-4-methyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	
3	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-7-(methylthio)quinoline	
4	7-chloro-4,8-dimethyl-2-(4-methyl-1,4-diazepan-1-yl)quinoline	
5	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-7-(methyloxy)quinoline	

Table 3

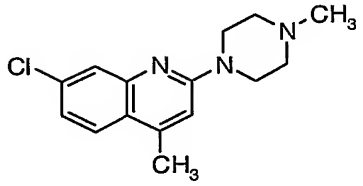
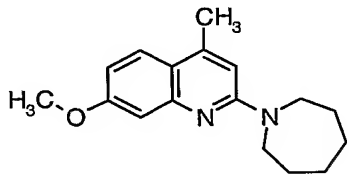
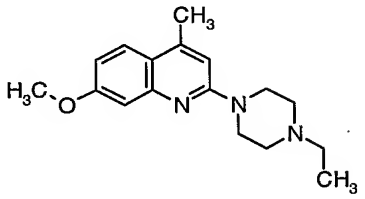
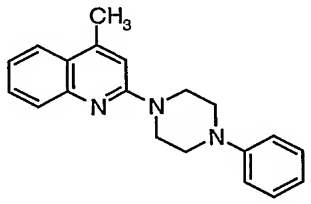
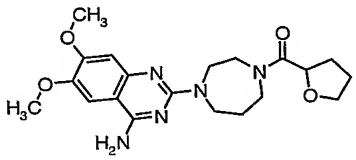
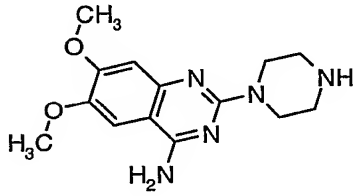
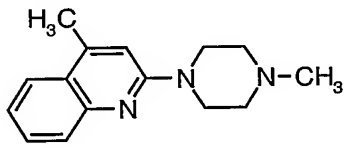
Entry	Name	Structure
6	7-chloro-4-methyl-2-(4-methylpiperazin-1-yl)quinoline	
7	2-azepan-1-yl-4-methyl-7-(methyloxy)quinoline	
8	2-(4-ethylpiperazin-1-yl)-4-methyl-7-(methyloxy)quinoline	
9	4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	
10	6,7-bis(methyloxy)-2-[4-(tetrahydrofuran-2-ylcarbonyl)-1,4-diazepan-1-yl]quinazolin-4-amine	
11	6,7-bis(methyloxy)-2-piperazin-1-ylquinazolin-4-amine	
12	4-methyl-2-(4-methylpiperazin-1-yl)quinoline	

Table 3

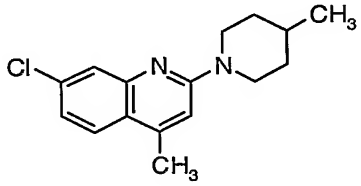
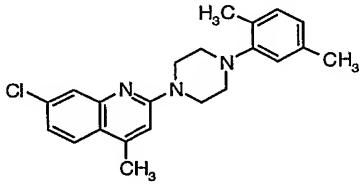
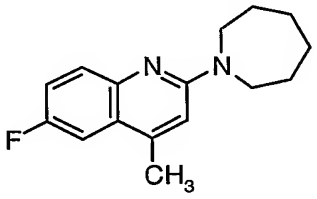
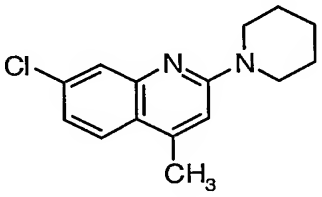
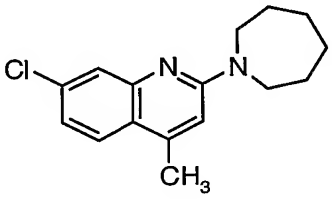
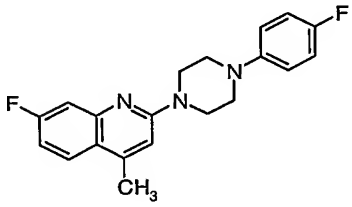
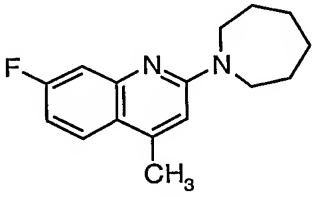
Entry	Name	Structure
13	7-chloro-4-methyl-2-(4-methylpiperidin-1-yl)quinoline	
14	7-chloro-2-[4-(2,5-dimethylphenyl)piperazin-1-yl]-4-methylquinoline	
15	2-azepan-1-yl-6-fluoro-4-methylquinoline	
16	7-chloro-4-methyl-2-piperidin-1-ylquinoline	
17	2-azepan-1-yl-7-chloro-4-methylquinoline	
18	7-fluoro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	
19	2-azepan-1-yl-4-methyl-8-(methyloxy)quinoline	

Table 3

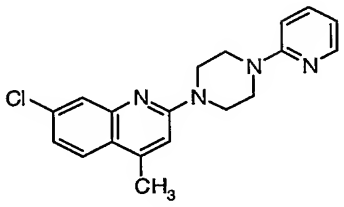
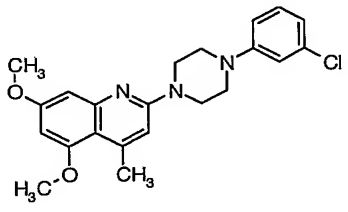
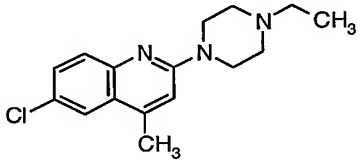
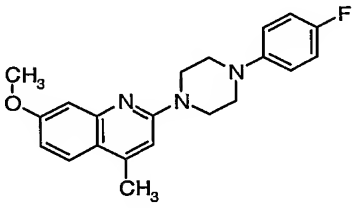
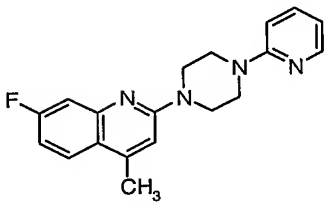
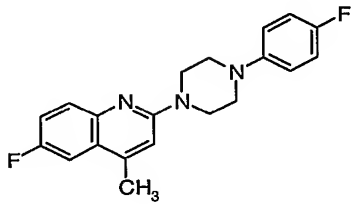
Entry	Name	Structure
20	7-chloro-4-methyl-2-(4-pyridin-2-ylpiperazin-1-yl)quinoline	
21	2-[4-(3-chlorophenyl)piperazin-1-yl]-4-methyl-5,7-bis(methyloxy)quinoline	
22	6-chloro-2-(4-ethylpiperazin-1-yl)-4-methylquinoline	
23	2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methyl-7-(methyloxy)quinoline	
24	7-fluoro-4-methyl-2-(4-pyridin-2-ylpiperazin-1-yl)quinoline	
25	6-fluoro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	

Table 3

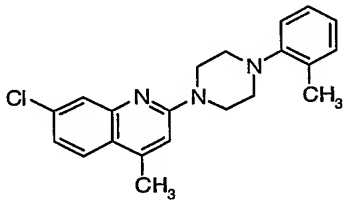
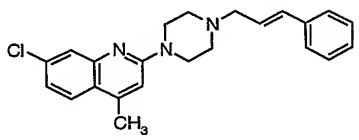
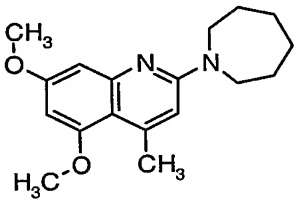
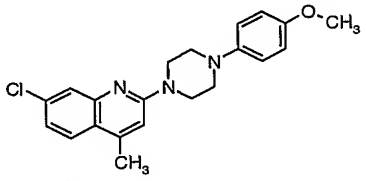
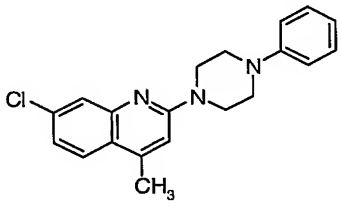
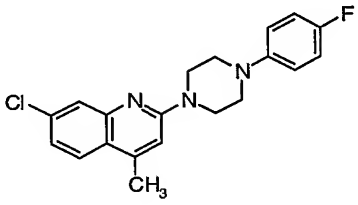
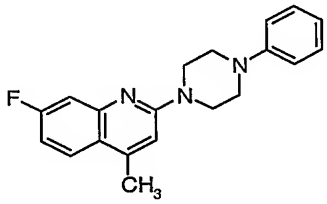
Entry	Name	Structure
26	7-chloro-4-methyl-2-[4-(2-methylphenyl)piperazin-1-yl]quinoline	
27	7-chloro-4-methyl-2-{4-[(2E)-3-phenylprop-2-en-1-yl]piperazin-1-yl}quinoline	
28	2-azepan-1-yl-4-methyl-5,7-bis(methyloxy)quinoline	
29	7-chloro-4-methyl-2-{4-[4-(methyloxy)phenyl]piperazin-1-yl}quinoline	
30	7-chloro-4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	
31	7-chloro-2-[4-(4-fluorophenyl)piperazin-1-yl]-4-methylquinoline	
32	7-fluoro-4-methyl-2-(4-phenylpiperazin-1-yl)quinoline	

Table 3

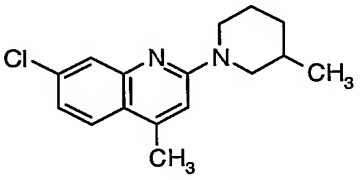
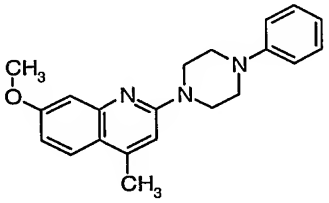
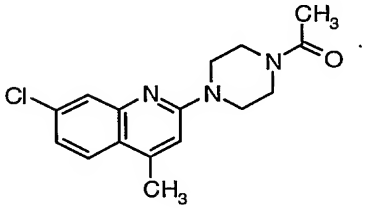
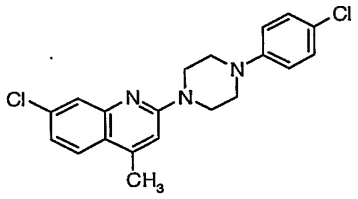
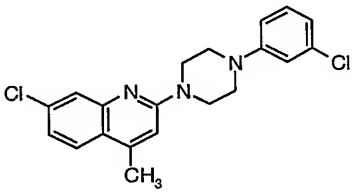
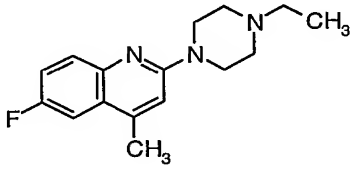
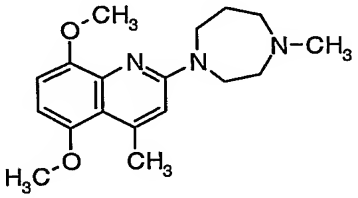
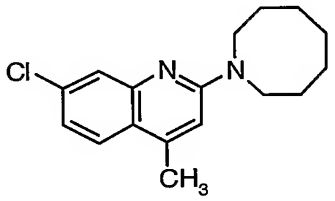
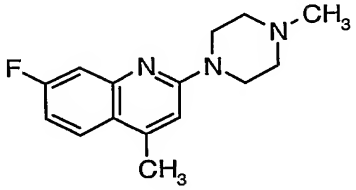
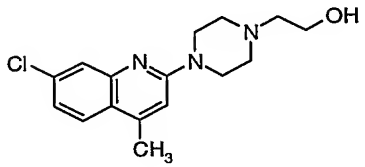
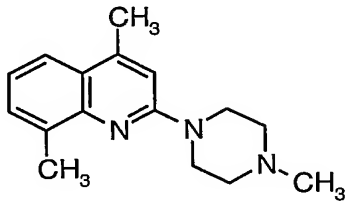
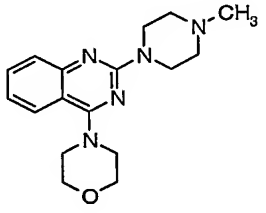
Entry	Name	Structure
33	7-chloro-4-methyl-2-(3-methylpiperidin-1-yl)quinoline	
34	4-methyl-7-(methyloxy)-2-(4-phenylpiperazin-1-yl)quinoline	
35	2-(4-acetylpiperazin-1-yl)-7-chloro-4-methylquinoline	
36	7-chloro-2-[4-(4-chlorophenyl)piperazin-1-yl]-4-methylquinoline	
37	7-chloro-2-[4-(3-chlorophenyl)piperazin-1-yl]-4-methylquinoline	
38	2-(4-ethylpiperazin-1-yl)-6-fluoro-4-methylquinoline	

Table 3

Entry	Name	Structure
39	4-methyl-2-(4-methyl-1,4-diazepan-1-yl)-5,8-bis(methyloxy)quinoline	
40	2-azocan-1-yl-7-chloro-4-methylquinoline	
41	7-fluoro-4-methyl-2-(4-methylpiperazin-1-yl)quinoline	
42	2-[4-(7-chloro-4-methylquinolin-2-yl)piperazin-1-yl]ethanol	
43	4,8-dimethyl-2-(4-methylpiperazin-1-yl)quinoline	
44	2-(4-methylpiperazin-1-yl)-4-morpholin-4-ylquinazoline	

15. A method of modulating the activity of metabolic kinases in pests, the method comprising administering to a pest an effective amount of a formulation comprising at least one example of the composition according to any of claims 1 - 14.

16. The method according to claim 15, wherein the kinase is EK.

17. The method according to claim 16, wherein modulating the activity of the kinase comprises inhibition of the kinase.

18. A method of controlling pests, the method comprising administering to a pest an effective amount of the composition according to any of claims 1 -14 or the formulation according to claim 15.

19. A kit comprising one or more containers filled with one or more of the compounds and/or compositions of according to any of claims 1 -14 or the formulation according to claim 15.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/07700

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 215/38; A61K 31/42
US CL : 546/157, 159; 504/247, 248
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 546/157, 159; 504/247, 248

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
East, West, Registry, Chemical Abstracts

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chem. abstr., Vol. 124, 1995 (Columbus, OH, USA), abstract No. 48290, KUZNETSOV, V.V. 'Synthesis and Pesticidal Activity of..." Khimiko-Farmatsevticheskii Zhurnal, 1995, 29(2), 61-62 (Russ).	1-55

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 July 2005 (05.07.2005)	22 JUL 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer D. Margaret Seaman Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (January 2004)